Armed Forces College of Medicine

AFCM

Treatment of Hyperlipidemia

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Cardiopulmonary module

INTENDED LEARNING OBJECTIVES (ILO

By the end of this lecture the student will be able to:

1-Discuss different drugs and diseases causing hyperlipidemias

2- List management of hyperlipidemia

3- Compare the mechanism of action , the adverse effects and drug interaction of statins and fibrates

4-Relate the therapeutic uses of statins and fibrates to their clinical applications

A patient 45 years old came to the c complaining of attacks of severe ch radiating to the left shoulder .

- On examination : **yellowish fatty deposits** were found on elbow ,knees, tendons, with history that they appeared many years ago. In addition to their appearance around the eyelids and on cornea. He gave a history that this condition had occurred before and was diagnosed as **stable angina** also he is **hypertensive** and on **Atenolol** and that his father was complaining of the same condition.
- Laboratory investigations revealed serum cholesterol 380 mg/dl and LDL 222 mg/dl.
- He was diagnosed as a case of stable angina with familial hypercholesterolemia.

Overview

- Coronary heart disease (CHD) is the leading cause of death worldwide.
- CHD is correlated with elevated levels of **low-density** lipoprotein **cholesterol** (**LDL-C; "bad" cholesterol**) and **triglycerides** and low levels of **high-density** lipoprotein cholesterol (**HDL-C; "good cholesterol**").
- Other risk factors for CHD include:

cigarette smoking, hypertension, obesity, and diabetes.

- Cholesterol levels may be elevated due to lifestyle

Overview

Hyperlipidemias can also result from:

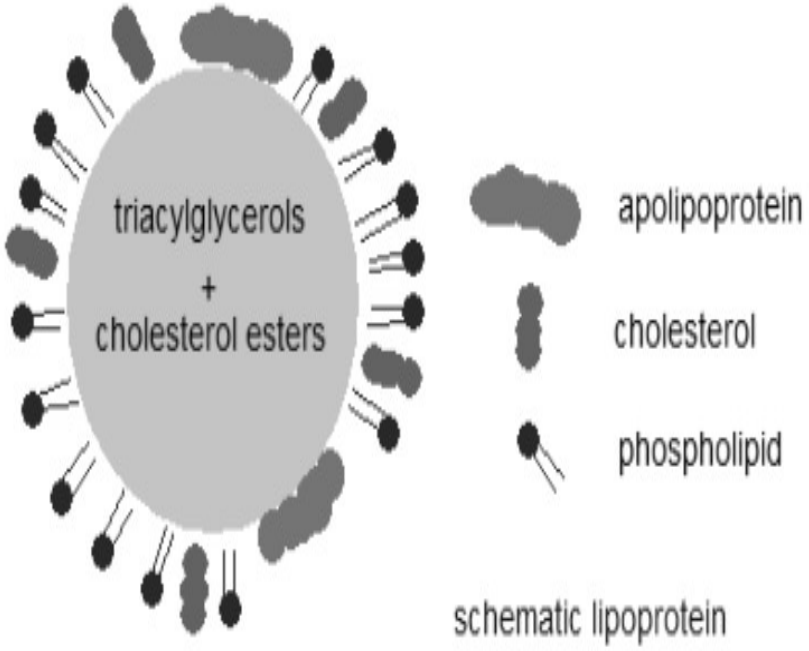
1. Primary: an inherited defect in lipoprotein metabolism (**Genetic**)
2. **life style factors** as **lack of exercise or diet containing excess saturated fats,** more commonly, from a combination of **Both**
3. **Secondary:**

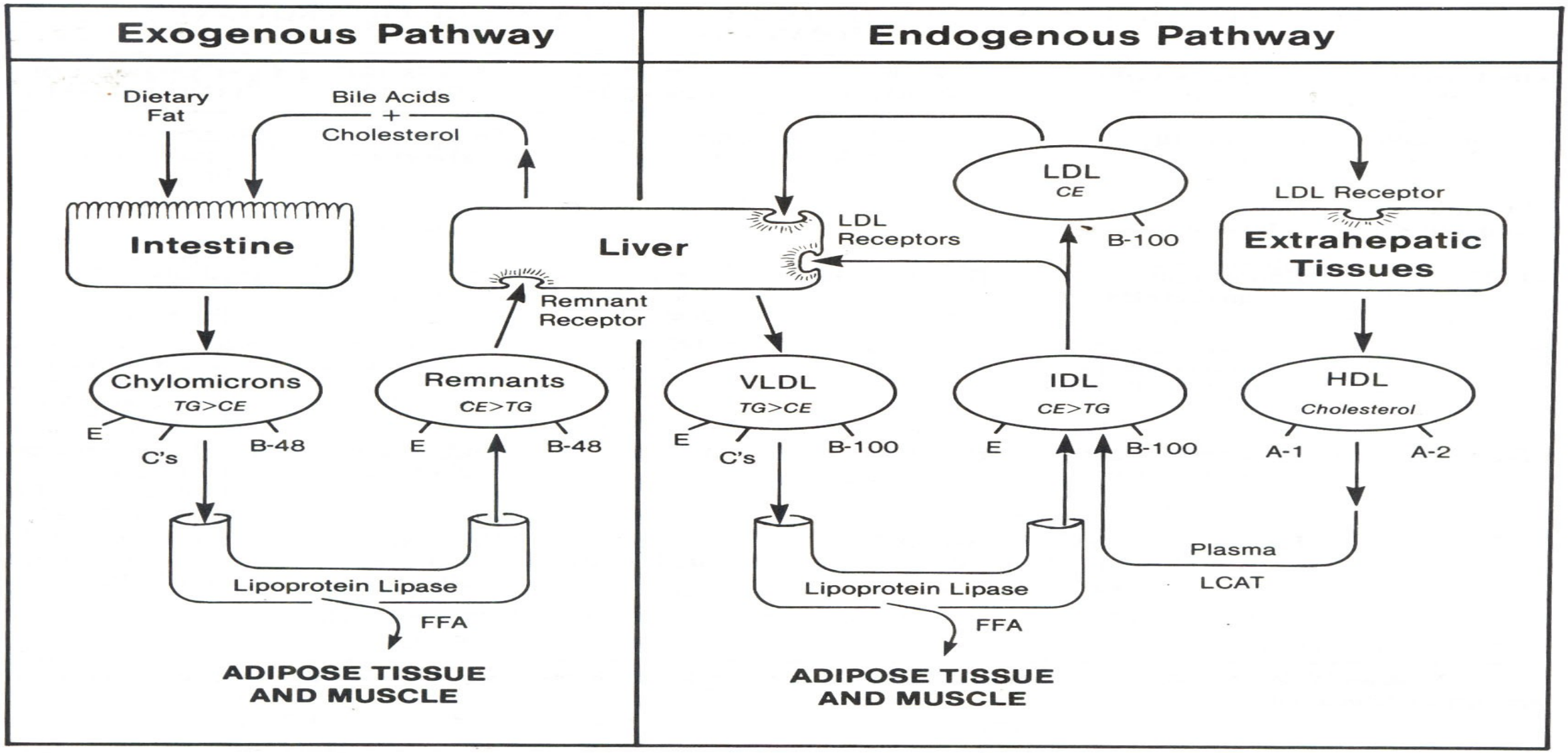
a- Diseases : DM, hypothyroidism, nephrotic syndrome, obesity.

Physiological Considerations:

1.Plasma lipoproteins

consist of **central core of Lipids** (triglycerides and cholesterol esters) encased in phospholipids, free cholesterol and proteins (called apolipoproteins).




Exogenous Pathway
Endogenous Pathway
Dietary Fat
Bile Acids + Cholesterol
Intestine
Liver
LDL Receptors
Remnant Receptor
LDL
CE
B-100
LDL Receptor
Extrahepatic Tissues
Chylomicrons
TG>CE
E
C's
B-48
Remnants
CE>TG
E
B-48
VLDL
TG>CE
E
C's
B-100
IDL
CE>TG
E
B-100
HDL
Cholesterol
A-1
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Lipoprotein Lipase
FFA
ADIPOSE TISSUE AND MUSCLE
Plasma
LCAT
Lipoprotein Lipase
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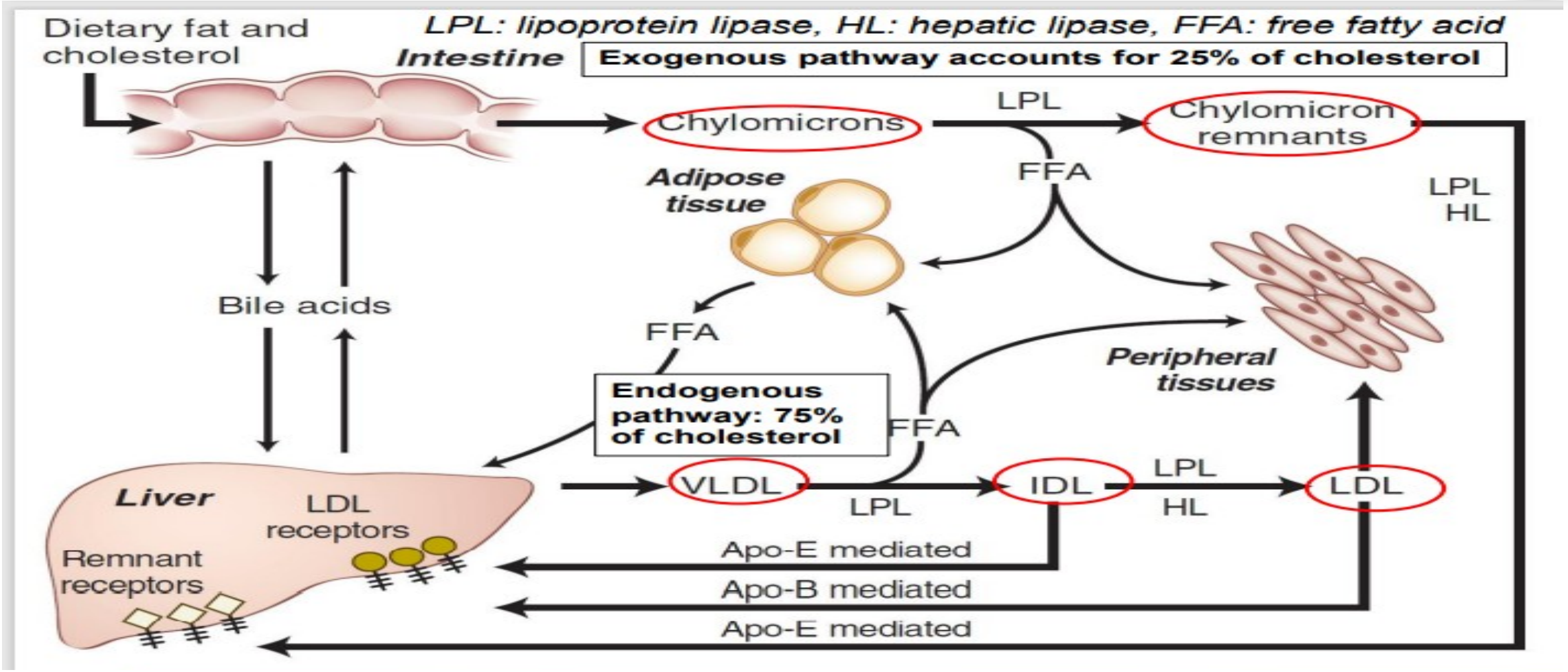
ADIPOSE TISSUE AND MUSCLE



http://www.med.swu.ac.th/Internalmed/images/documents/lectures/endocrine/brian/slide/dyslipidemia.pdf

MANAGEMENT OF HYPERLIPIDEMIAS

I. Diet

1. **Avoid saturated fatty acids** (animal fats).

2. **Give unsaturated fatty acids** (plant fats), e.g. olive oil, sunflower oil:

Polyunsaturated FAs increase conversion of free cholesterol (metabolically active) to cholesterol ester (inactive) □ □ hepatic free cholesterol □ compensatory □ LDL receptors □ □ uptake of LDL □ □ plasma LDL

3. **Regular fish oil in diet**: contain

II. Exercise

4. **Vitamins E & C** (antioxidants).

□ HDL

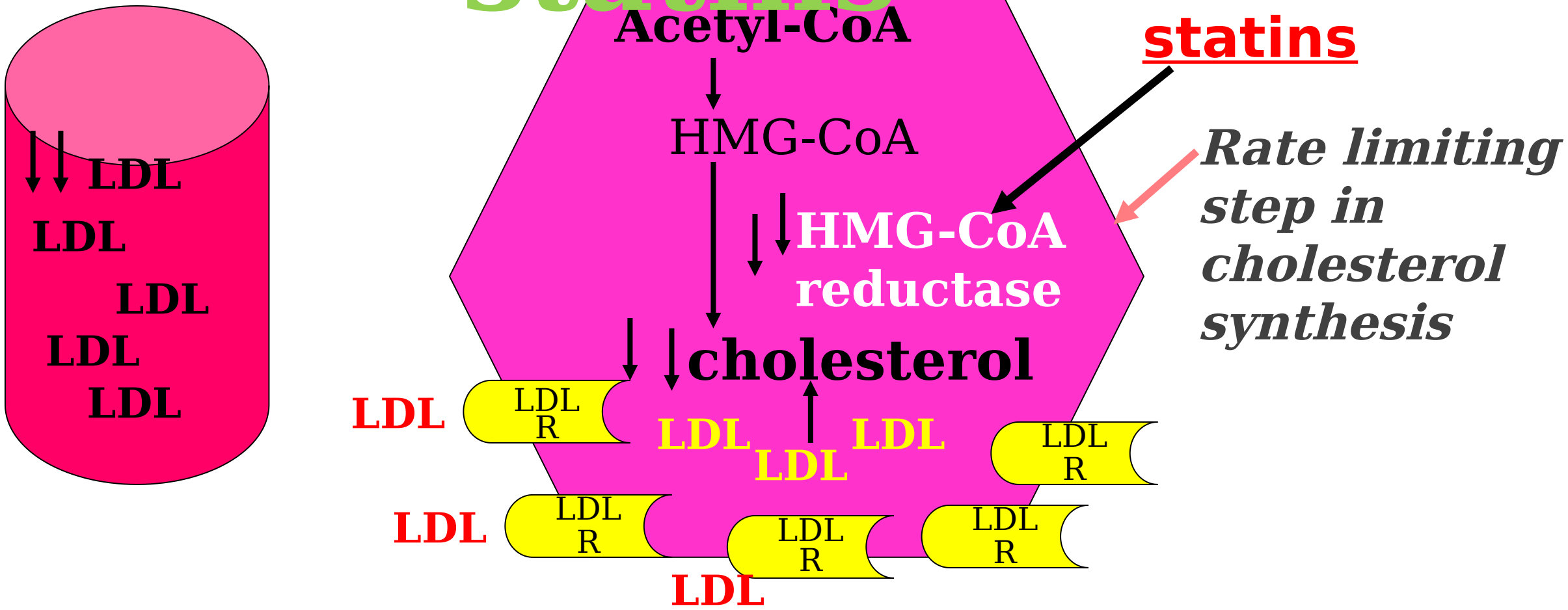
□ insulin sensitivity delaying maturity-onset DM.

III. Drug Therapy

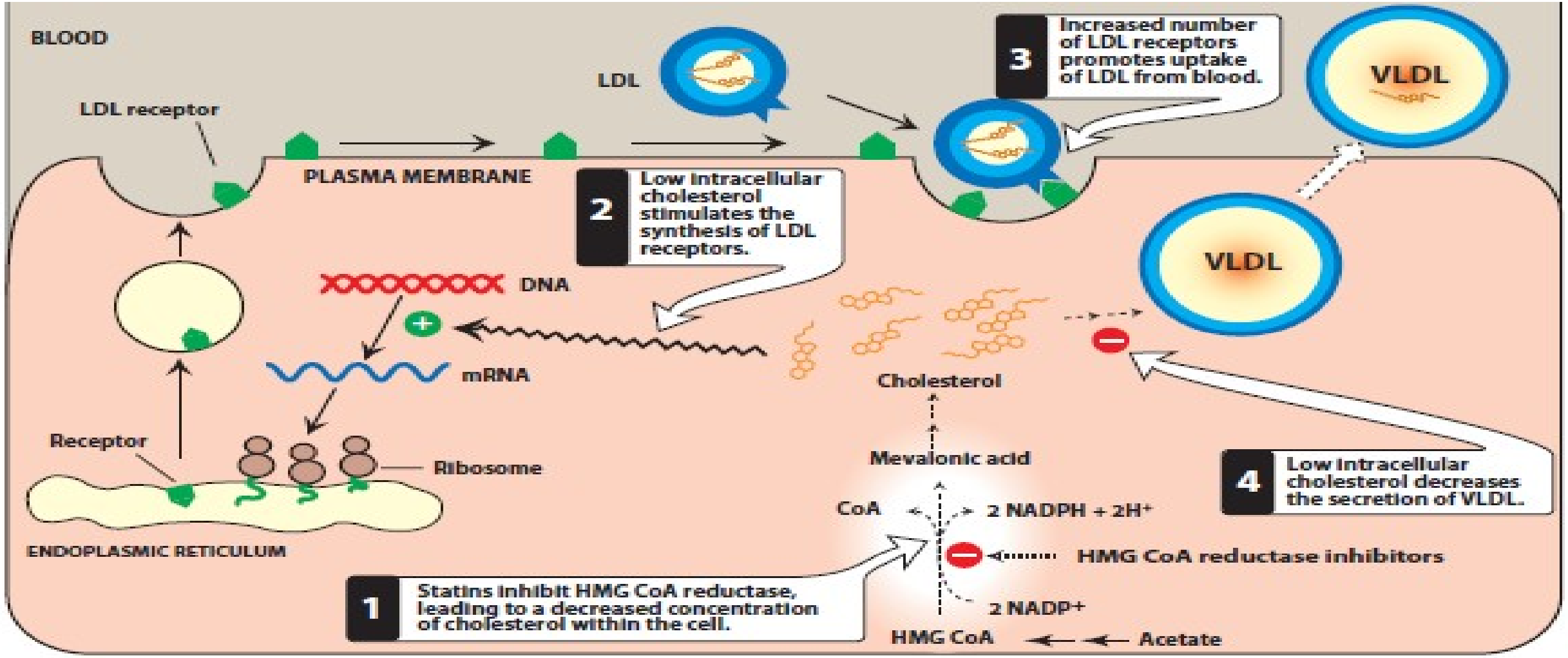
Used when dietary and risk factor management fails.

I-

MECHANISM statins



MECHANISM



Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

Mechanism of action.

a. Statins act by competitively inhibiting HMG-CoA reductase

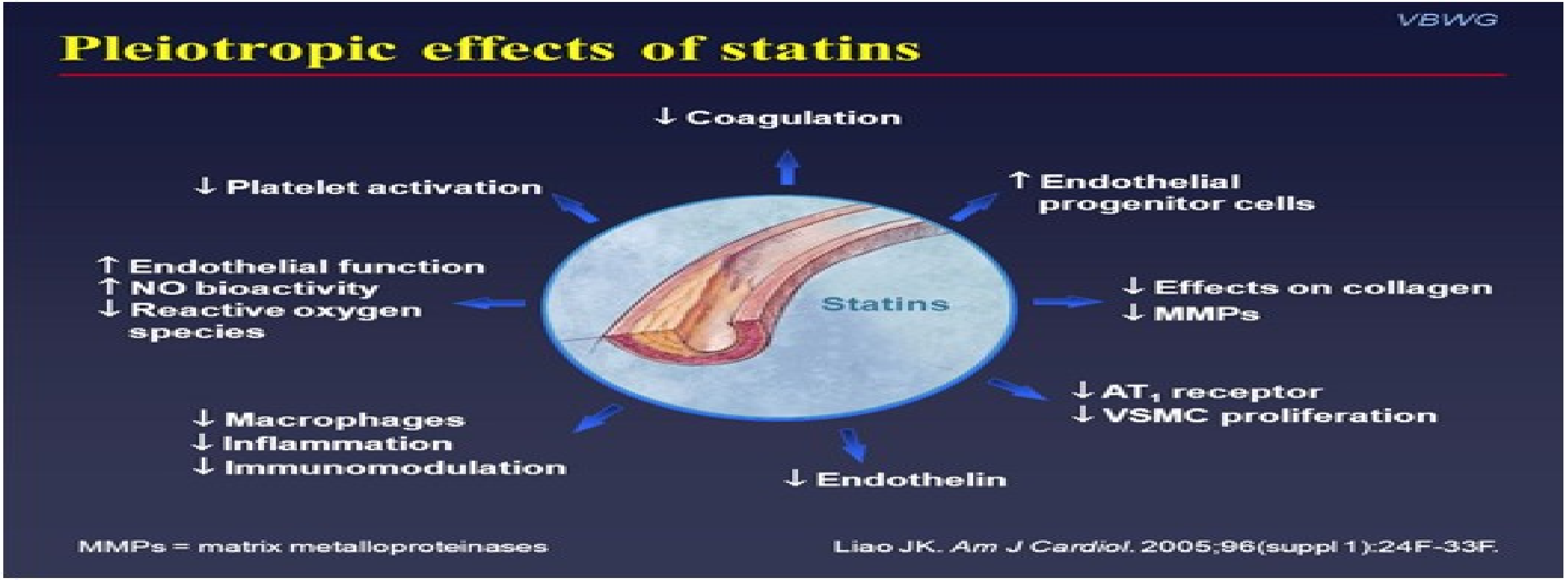
b. HMG-CoA reductase is the rate-controlling enzyme of the mevalonate pathway, the metabolic pathway that produces cholesterol in the liver

Depletion of intracellular cholesterol→ Number of LDL receptors on liver cells

1. LDL cholesterol in plasma
2. Plasma HDL levels.
3. Plasma triglycerides

e-Some actions of statins are unrelated, or indirectly related, to their effect on plasma lipid "Pleiotropic effects".

Such actions include: improved endothelial function, reduced vascular inflammation, reduced platelet



Pharmacokinetics:

a. Absorbed orally.

b. . Half-lives range variable (1-3 hours) so All statins are taken orally at *bedtime* because of diurnal rhythm of cholesterol synthesis, except atorvastatin , Ro

because of their long half-life (14 ,19,12 hours respectively).

c. First pass effect, so primary action on liver.

Lovastatin and simvastatin are hydrolyzed to the active drug.

The remaining statins are administered in their active form

Uses:

e.g:

Because these agents undergo a marked first-pass extraction by the liver, their dominant effect is on that organ

- **Pitavastatin**
- **Atorvastatin**
- **Rousavastatin**
- **Lovastatin**
- **Simvastatin**
- **Pravastatin**
- **Fluvastatin**

Familial or non *Hypercholesterolemia*

Initiate reductase inhibitor therapy immediately after acute coronary syndromes, *regardless* of lipid levels.

Side effects

- **1-Hepatotoxicity: often intermittent**

↑↑serum transaminases up to three times normal

.2-Myopathy & myositis: Besides muscle pain, the other major symptom of rhabdomyolysis is dark, red, or cola colored urine)

↑↑ serum creatine kinase

Interactions:

1-Potentiate the action of oral anticoagulant (by effect on platelet function) and antidiabetic drugs (displacement from plasma protein binding sites).

2- *Most* of the statins are metabolized through the cytochrome P450 (CYP) metabolic pathway; and inhibitors of this enzyme may increase the risk of rhabdomyolysis.

3- In contrast, pravastatin (Pravachol) and rosuvastatin (Crestor) do not depend on the CYP450 pathway.

Contra-indications:

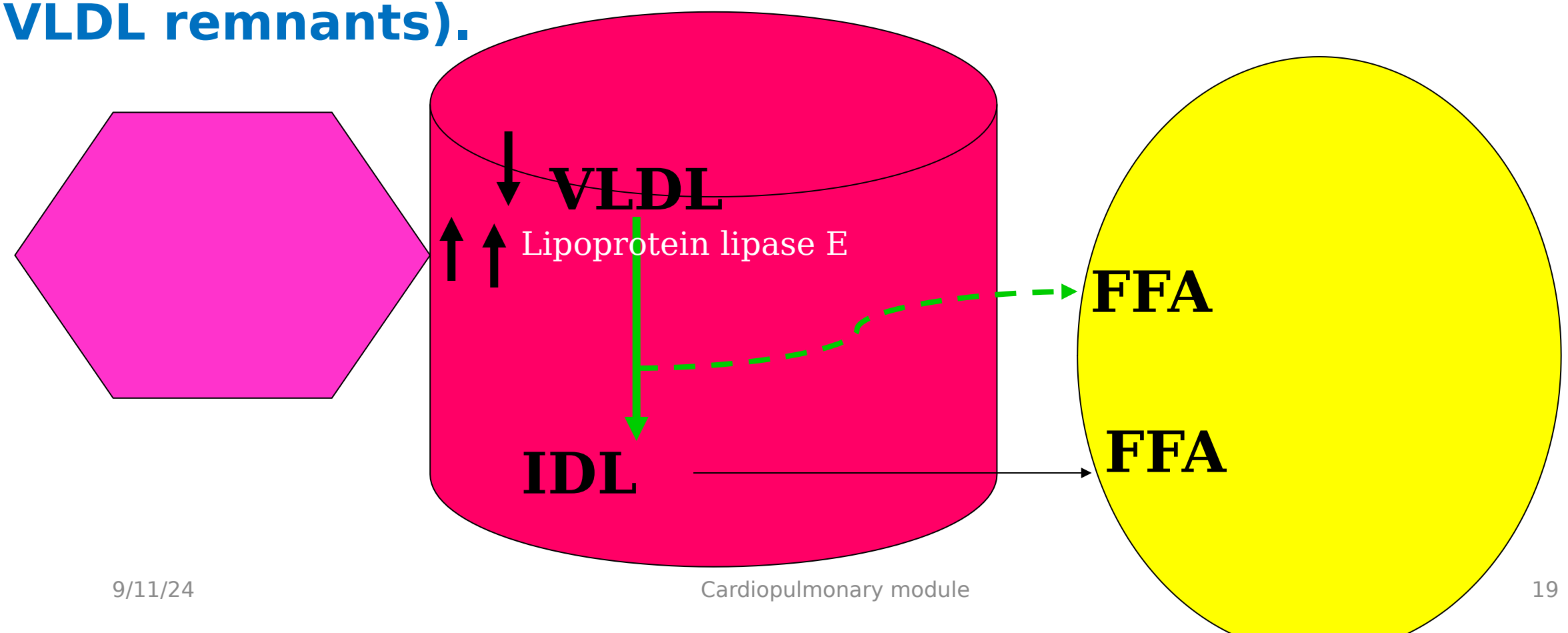
pregnancy and lactation

(cholesterol is important for normal development, and it is possible that statins could cause serious problems).

II-Fibrates

MECHANISM

Increased catabolism of serum TG-rich proteins (VLDL and VLDL remnants).

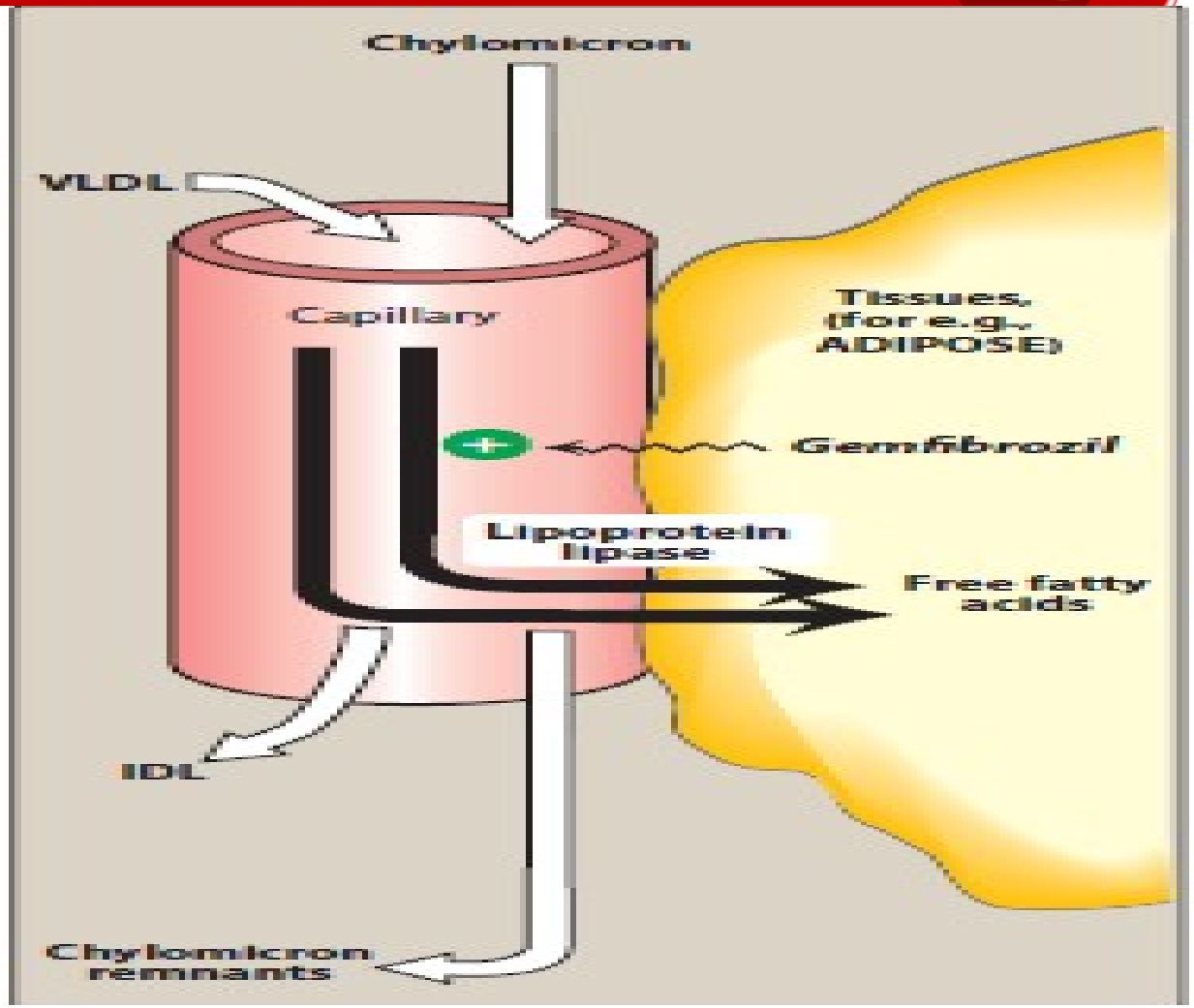


Mechanism of action:

a. **Fibrates are agonists for peroxisome proliferator-activated receptor α (PPAR alpha) in muscle, liver, and other tissues.**

b. Activation of PPAR-α signaling results in: transcriptionally up-regulatation of LPL, apo A-I and apo A-II.

-Increased lipoprotein lipase activity → ↑hydrolysis of TG →



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Pharmacokinetics:

1. ***Gemfibrozil*** **and** ***fenofibrate*** **are completely absorbed after oral administration distribute widely and improved when taken with food, but** ***Fenofibrate*** **is more effective than** ***gemfibrozil*** **in lowering triglyceride levels.**
2. **bound to albumin.**
3. **Fenofibrate is a prodrug, which is converted to the active fenofibric acid.**
4. **Fibrates are metabolized in the kidney and should be avoided or used with caution in patients with kidney disease , excreted in the urine.**
5. **Pemafibrate is a selective PPAR-α modulator Selective peroxisome proliferator-activated receptor α modulators (SPPARM-α), a newer, more potent fibrate.**

Uses:

e.g:

- **Fenofibrate**
- **Gemfibrozil.**
- **Pemafibrate**

Familial

Hypertriglyceridemia

Mixed hyperlipidemia.

Non

Side effects

1. **GIT upset** (**most common**).
2. **Cholesterol gall stone formation** (since fibrates increase the **biliary cholesterol excretion**), cholecystitis.
3. **Myopathy and myositis** →**elevated CK** especially when combined with statins.
4. **hepatotoxic** (elevated liver enzymes).

Interactions:

Potentiate the action of

1. oral anticoagulant (decrease fibrinogen)
2. antidiabetic drugs

(displacement from plasma protein binding sites also, it stimulates B- oxidation in skeletal muscles improving glucose metabolism.)

Contra-indications:

a. Pregnancy and lactation.

b. Gall-bladder disease.

c. Hepatic and renal dysfunction.

SUGGESTED TEXTBOOKS

1- Whalen, K., Finkel, R., & Panavelil, T. A. (2018) Lippincott's Illustrated Reviews: Pharmacology (7th edition.). Philadelphia: Wolters Kluwer

2- Katzung BG, Trevor AJ. (2018). Basic & Clinical Pharmacology (14th edition) New York: McGraw-Hill Medical.

THANK YOU